REMARKS

Claims 39-43 and 74-108 are pending. Claims 1-38, 42, 44-73, 75-76, 80-84 and 108 are canceled without prejudice. Claims 39-41, 43, 74 and 85-104 are currently amended. New claims 109-111 are added. No new matter is added by this amendment.

Applicants wish to thank Examiner Belyavskyi for participating in a telephonic interview on August 23, 2006. During the interview the outstanding 35 U.S.C. §103(a) rejections of claims 39-41, 43, 74, 77-79, 81, 83 and 85-108 over WO 97/15310, WO 00/09666 or WO 02/0861107 were discussed. Applicants presented data demonstrating that the WO '310 application does not teach an isolated nestin-positive human pancreatic stem cell according to the invention. During the interview the applicability of WO 00/09666 and WO 02/0861107 was also discussed.

Rejection of Claims 39-41, 43, 74, 77-79, 81, 83 and 85-108 under 35 U.S.C. §112, first paragraph

The Examiner states at page 2 of the Office Action that "[a]n isolated composition comprising at least 30% nestin positive..." claimed in claims 39-41, 43, 74, 77-79, 81, 83 and 85-108 represent a departure from the specification and the claims as originally filed."

Applicants submit that claims 77-79 and claims 105-107 do not related to an isolated composition.

Claims 81, 83 and 108 have been cancelled.

Applicants submit that claims 39, 40, 41, and 85-104 have been amended to delete the phrase "composition comprising at least X%" (wherein X is one of 30, 40, 50, 60, 70, 80, 85, 90, 95 or 99%). Amended claims 39, 40, 41, 43 and 85-104 now refer to "an isolated nestin-positive human pancreatic or liver stem cell that is not a neural stem cell wherein said stem cell is at least X% pure (wherein X is one of 30, 40, 50, 60, 70, 80, 85, 90, 95 or 99%).

Claims 43 and 74 have been amended to depend from new claims 109, 110 and 111,

relating to an isolated nestin-positive or GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell.

In view of the above, Applicants request reconsideration and withdrawal of the rejection.

Rejection of Claims 39-41, 43, 74, 77-79, 81, 83 and 85-108 under 35 U.S.C. §103(a)

Claims 39-41, 43, 74, 77-79, 81, 83 and 85-108 are rejected under 35 U.S.C. §103(a) for alleged obviousness over WO 97/15310, WO 00/09666, or WO 02/0861107.

Applicants respectfully traverse the rejections.

Applicants submit that claims 81, 83 and 108 are cancelled.

For the reasons described below, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. Finally, the prior art reference (or references when combined) must teach or suggest ***all the claim limitations***. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

WO '310

The Examiner states at page 3 of the Office Action that "WO'310 teaches an isolated nestin-positive human pancreatic stem cell[s] that are not a neural stem cell[s] that can differentiate to form insulin-producing cells...WO'310 teaches a pharmaceutical composition comprising said cells in cultured media or in PBS, that is a physiologically compatible carrier...WO'310 teaches several methods of isolating pancreatic stem cells comprising steps of

removing a pancreatic islet from the donor and separating stem cells from plurality of cells...[t]he method of isolating said cells is substantially similar to that used by applicant...[w]hile WO'310 does not specifically teach that these cells are GLP-1R-positive cells, said cells would obviously be GLP-1R positive cells, since the cell population taught by WO'310 is identical to that claimed in the instant application."

Applicants submit that the invention of the WO '310 application "concerns the discovery that functional islets containing insulin-producing β-cells, as well as other islet cell types, can be grown in long-term cultures from pluripotent stem cells, which give rise to islet producing stem cells, IPSCs" (see page 8, lines 27-30). The WO '310 application discloses at page 12, lines 21-23 that "IPSCs are a small population of cells derived from ductal epithelial cells (i.e., these cells are pancreas-derived but are not differentiated islet cells)".

The WO '310 application teaches a method of growing IPSCs at page 13 line 29 through page 14, line 25 wherein it is stated that,

> " [t]he method of the subject invention involves making suspensions of cells, including stem cells, from the pancreas of a mammal. . .The cell suspensions are prepared using standard techniques. The cell suspension is then cultured in a nutrient medium that facilitates the growth of the IPSCs, while at the same time severely compromising the sustained growth of the differentiated or mature cells other than IPSCs. . . What is required for such media is that they have little or no glucose (less than about 1 mM) and low serum (less than about 0.5%). The high amino acid concentrations are preferably of amino acids known to be essential for the cells of the species being cultured, and provide a carbon source for the cultured cells. In addition, at least one rudimentary lipid precursor, preferably pyruvate, is provided. These conditions are so stressful to most differentiated cell types that they do not survive. Surprisingly, however, upon extended culture of cells from pancreatic tissue without re-feeding (about 3 weeks) IPSCs do survive and after extended culture, begin to proliferate."

As presented in the attached Declaration of Dr. Abraham, at no time do the cultures of the '310 reference have "an isolated nestin-positive human pancreatic stem cell that is not a neural cell" or "an isolated GLP-1R-positive human pancreatic stem cell" as required by claims 39-41, 43, 74, 77-79, 85-107 and new claims 109-111.

As disclosed in the instant specification at page 16, lines 1-13 of the instant specification, "isolated" is defined as follows:

> "Isolating" a stem cell refers to the process of removing a stem cell from a tissue sample and separating away other cells which are not stem cells of the tissue. An isolated stem cell will be generally free from contamination by other cell types and will generally have the capability of propagation and differentiation to produce mature cells of the tissue from which it was isolated. However, when dealing with a collection of stem cells, *e.g.*, a culture of stem cells, it is understood that it is practically impossible to obtain a collection of stem cells which is 100% pure. Therefore, an isolated stem cell can exist in the presence of a small fraction of other cell types which do not interfere with the utilization of the stem cell for analysis or production of other, differentiated cell types. Isolated stem cells will generally be at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99% pure. Preferably, isolated stem cells according to the invention will be at least 98% or at least 99% pure."

To demonstrate that the WO '310 reference does not give teach "an isolated nestin-positive human pancreatic stem cell" or "an isolated GLP-1R positive human pancreatic stem cell" as required by the instant claims, Dr. Abraham attempted to obtain an isolated nestin-positive or GLP-1R positive human pancreatic stem cell of claims 39-41, 43, 74, 77-79, 85-107, and new claims 109-111, using the culture conditions described in the WO '310 reference. As noted by Dr. Abraham, there are substantial differences between the culture conditions described in the specification to achieve the population of cells of the instant claims, and the culture conditions described in the WO '310 reference. A table highlighting these differences is reproduced as Exhibit A to the Abraham declaration. Exhibit A compares the media, serum, growth factors and culture conditions described in the present specification against those described in the WO '310 reference. For example, the '310 reference does not teach culture conditions wherein immediately following trypsinization of islets, cells are cultured in media in the presence of glucose, high serum and growth factors.

The Declaration of Dr. Abraham presents data demonstrating the following. Upon receipt of a human islet (H1085) from Edmonton, Canada, the tissue (1000 Islet Equivalents (IEQs)) was trypsinized and 3.5 million cells were obtained. According to the method described in the '310 application at pages 26, line 1, through page 29, line 3, the cells were plated in six T-25 flasks in DMEM (no glucose and 0.25% FBS) without re-feeding for a period of three weeks. Within the first few days of culture there were very few attached cells. At the end of the three week period only cell debris was visible (Exhibit B). At four weeks the cultures were divided

and re-fed with either Click's medium, supplemented with 0.5% FBS or RPMI supplemented with 10% FBS, bFGF and EGF (three flasks of each). Cultures were monitored for an additional two week period. No cells survived under either condition. Exhibit B presents representative photomicrographs taken 3.5 weeks after the initiation of the cultures. Virtually no live cells are present. The majority of what is detected is cell debris. All dead cell clumps and cell ghosts are non-adherent and appear necrotic. A-D represent four individual culture flasks. In panel A, dark necrotic cell clumps are indicated by the arrows. In panels B and C, cell debris and dead non-adherent cell clumps floating in suspension are indicated by the arrows. In panel D there is only cell debris with no live adherent cells in culture. Applicants have therefore been unable to reproduce the results presented in the WO '310 application. The data presented herein presents the results obtained with four replicate samples of a single islet isolate. The experiment described herein was performed twice with two separate islet isolates as starting material (data not shown for second experiment). The same results (no viable cells) were obtained in both experiments.

In the Office Action dated December 2, 2004 the Examiner stated at page 4 that "[s]ince the office does not have a laboratory to test the reference isolated nestin-positive human pancreatic stem cells, it is applicant's burden to show that the reference nestin-positive human pancreatic stem cells do not have the functional limitation as recited in the claims."

Applicants have met the burden of showing that the reference cells do **not** have the functional limitation as recited in the claims. Applicants were unable to produce any viable cells, and in particular any viable nestin-positive or GLP-1R positive human pancreatic stem cells using the method of cell isolation presented in the WO '310 application. Therefore, the reference cells described in the WO '310 application are not nestin-positive or GLP-1R positive human pancreatic stem cells as required by the instant claims. Applicants respectfully submit that the burden to show that the reference cells are nestin-positive pancreatic stem cells as required by the instant claims is shifted back to the office.

Applicants previously filed a Rule 1.132 declaration of Dr. Habener providing evidence that only 0.2-5% of the cells of the pancreas are nestin-positive cells (see part 5 of the Rule 1.132 filed with Applicant's response to the Office Action dated December 23, 2003).

In Applicants response to the Office Action dated December 23, 2003 Applicants asserted that "[g]iven the very low percentage of nestin-positive stem cells in the pancreas, one of skill in the art would not accept that the method of growing stem cells presented in the WO '310 application would result in an isolated nestin-positive or GLP-1R-positive pancreatic stem cell as required by claims 39-43 and 74 of the instant application, since this method lacks a step wherein nestin-positive or GLP-1R-positive stem cells are isolated. In view of the above, Applicants respectfully assert that one of skill in the art would not accept that the suspension of stem cells grown according to the method described in the WO '310 application is an isolated nestin-positive or GLP-1R positive human pancreatic stem cell as required by instant claims 39-43."

In Applicant's response to Office Action dated December 2, 2004, Applicants asserted that "[g]iven the small percentage of nestin-positive and GLP-1R positive cells in the pancreas (either in the islets or the ducts), one of skill in the art would not accept that...the WO '310 application teach a composition comprising at least 30% isolated nestin-positive or GLP-1R positive human pancreatic stem cells since none of these applications teach an isolated nestin or GLP-1R positive human pancreatic or liver stem cell that is not a neural stem cell, as defined in the instant application."

As stated in the attached Rule 1.132 declaration of Dr. Habener, Applicants did not mean to imply that the WO '310 application discloses even a small percentage of nestin-positive or GLP-1R positive pancreatic stem cells. In fact, in view of the experimental results presented in the attached Rule 1.132 declaration of Dr. Abraham and discussed herein, Applicants now assert that the WO '310 application does not teach any of an isolated nestin positive or GLP-1R positive human pancreatic stem cell or an isolated nestin-positive or GLP-1R positive human pancreatic stem cell, wherein the stem cell is at least 30, 40, 50, 60, 70, 80, 85, 90, 95 or 99% pure, as required by the instant claims. In fact, when Applicants used the experimental methods

presented in the WO '310 application for obtaining cells from a pancreas, no viable cells were obtained.

In view of the above, the WO '310 reference does not teach any of "an isolated nestin or GLP-1R-positive human pancreatic stem cell", or an isolated nestin-positive or an isolated GLP-1R positive human pancreatic stem cell, wherein the cell is at least 30, 40, 50, 60, 70, 80, 85, 90, 95 or 99 % pure, as required by the instant claims. In view of the above, the instant claims are patentable over the WO '310 reference.

WO '666

The Examiner states at page 4 of the Office Action that "WO '666 teaches an isolated nestin-positive, human pancreatic stem cell[s] that can differentiate to form insulin-producing cells...WO '666 teaches that said cell[s] is also GLP-1R positive...WO'666 teaches a pharmaceutical composition comprising said cells in cultured media or in PBS, that is a physiologically compatible carrier...WO'666 teaches several methods of isolating said cells."

Claims 39, 85-94 and new claim 109 relate to an isolated nestin-positive human pancreatic stem cell. Claims 40, 43, 74, 77-79, 95-107 and 110-111 relate in part to an isolated nestin-positive human pancreatic stem cell.

Support for the subject matter of claims 39, 85-94 and 109, and the subject matter of claims 40, 43, 74, 77-79, 95-107 and 110-111 that relates to an isolated nestin-positive human pancreatic stem cell is found in the instant application, as well as in the following priority documents: U.S. Provisional Application No. 60/169,082, filed December 6, 1999, U.S. Provisional Application 60/215,109, filed June 28, 2000, and U.S. Provisional Application 60/238,880, filed October 6, 2000. The effective filing date for claims 39, 85-94 and 109, and for the subject matter of claims 40, 43, 74, 77-79, 95-107 and 110-111 that relates to an isolated nestin-positive human pancreatic stem cell is therefore December 6, 1999.

As discussed in the Manual of Patent Examining Procedure (see section 706.02(f)(1)) WIPO publications of International Applications filed before November 29, 2000 are applied as of their publication date and not as of their international filing date.

The WO '666 application has an international filing date of August 10, 1999. Therefore, the WO '666 application can be applied as of its publication date of February 24, 2000. In view of the above, the WO '066 application is not prior art to the invention as claimed in claim 39, 85-94, 109 and to the subject matter of claims 40, 43, 74, 77-79, 95-107 and 110-111 that relates to an isolated nestin-positive human pancreatic stem cell.

Claims 40, 41, 43, 74, 77-79, 95-107 and 110-111 include the limitation of an isolated, GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell.

Applicants have attached a Rule 1.131 declaration from Dr. Habener demonstrating that the subject matter of claims 40, 41, 43, 74, 77-79, 95-107 and 110-111 was conceived prior to the publication of the WO '666 application.

In view of the above, Applicants submit that claims 39-41, 43, 74, 77-79, 85-107, and new claims 109-111 are patentable over the '666 application and respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection.

WO '107

The WO 02/086107 publication teaches differentiation of stem cells, wherein the stem cells are preferably ES or EG cells (see page 5, lines 4-5 wherein the WO '107 publication states that "[t]he present invention is aimed at inducing the differentiation of ES cells by activation of specific genes into insulin-producing cells"; page 8, lines 25-27, " 'cultivation medium' means a suitable medium capable of supporting growth and differentiation of stem cells, preferably ES and EG cells"). The WO 02/086107 also discloses a method of differentiating ES cells into insulin-producing cells using culture conditions that favor the formation of nestin-positive cells (see Example 8, page 27 through 28) as well as a method of selecting nestin-positive cells from embryoid bodies (see page 13, lines 11-17). This publication does not teach a stem cell isolated from a pancreas.

Claims 39, 85-94 and new claim 109 relate to an isolated nestin-positive human pancreatic stem cell. Claims 40, 43, 74, 77-79, 95-107 and 110-111 relate in part to an isolated nestin-positive human pancreatic stem cell.

Support for the subject matter of claims 39, 85-94 and 109 and the subject matter of claims 40, 43, 74, 77-79, 95-107 and 110-111 that relates to an isolated nestin-positive human pancreatic stem cell is found in the instant application, as well as in the following priority documents: U.S. Provisional Application No. 60/169,082, filed December 6, 1999, U.S. Provisional Application 60/215,109, filed June 28, 2000, and U.S. Provisional Application 60/238,880, filed October 6, 2000. The effective filing date for claims 39, 85-94 and 109 and for the subject matter of claims 40, 43, 74, 77-79, 95-107 and 110-111 that relate to an isolated nestin-positive human pancreatic stem cell is therefore December 6, 1999.

The WO '107 application has an international filing date of April 19, 2002, and claims priority to a provisional application filed on April 19, 2001. Therefore, the WO '666 application can be applied as of its earliest priority date of April 19, 2001. In view of the above, the WO '107 application is not prior art to the invention as claimed in claims 39, 85-94 and 104, and to the subject matter of claims 40, 43, 74, 77-79, 95-107 and 110-111 that relates to an isolated nestin-positive human pancreatic stem cell.

Claims 40, 41, 43, 74, 77-79, 95-107 and 110-111 include the limitation of an isolated, GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell.

Applicants have attached a Rule 1.131 declaration from Dr. Habener demonstrating that the subject matter of claims 40, 41, 43, 74, 77-79, 95-107 and 110-111 was conceived prior to the publication of the WO '107 application.

In view of the above, Applicants submit that claims 39-41, 43, 74, 77-79, 85-107, and new claims 101-111 are patentable over the '107 application and respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection.

In view of all of the above, Applicants submit that claims 39-41, 43, 74, 77-79, and 85-111 are patentable over the WO 97/15310, WO 00/009666, and WO 02/086107 applications.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection.

CONCLUSION

Applicants submit that in view of all of the above, all claims are allowable as written and respectfully request early favorable action by the Examiner.

Respectfully submitted,

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